PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	14 SEP 2007
Applicant's or agent's file reference 10159 -- PCT	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US05/00638	07 January 2005 (07.01.2005)	07 January 2004 (07.01.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC: **C12Q 1/00**(2006.01),**1/68**(2006.01) C07K 1/00(2006.01)
USPC: 435/4,6,7.1

Applicant

BRISTOL-MYERS SQUIBB COMPANY

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis(b)* that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	03 July 2007 (03.07.2007)	Susan Ungar Telephone No. 571-272-0837

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/00638

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☒ on paper

☒ in electronic form

c. time of filing/furnishing

☒ contained in the international application as filed.

☒ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/00638

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
   - ☐ paid additional fees
   - ☐ paid additional fees under protest and, where applicable, the protest fee
   - ☐ paid additional fees under protest but the applicable protest fee was not paid
   - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1-in-part, 2, 3-in-part

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/00638

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-in-part, 2, 3-in-part	YES
	Claims NONE	NO
Inventive step (IS)	Claims 1-in-part, 2, 3-in-part	YES
	Claims NONE	NO
Industrial applicability (IA)	Claims 1-in-part, 2, 3-in-part	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:
Claims 1-in-part, 2, 3-in-part an inventive step under PCT Article 33(3) as being obvious over NORMANNO ET AL.Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR-TKIs) ; Simple Drugs with a Complex Mechanism of Action? Journal of Cell Physiol. 2002. Vol 194. pgs 13-19 in view of WONG ET AL. BBRC. 2003. Vol 311. pgs 618-624, and SLESAK ET AL. Anticancer Research. 1998, Jul-Aug : Vol. 18(4A)2727-2732

The claims are drawn to a method a method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering an EGFR modulator, wherein the method comprises measuring in the mammal the level of SEQ ID NO:1, cadherin 17, wherein a difference in level of SEQ ID NO:1 is indicative that the mammal will respond to said method of treating cancer.

Normanno et al teach that cytotoxic drugs are not able to achieve the several logs of cell kill that are required to disrupt solid neoplasms, are highly toxic to normal tissues and treatment for long periods is not tolerable for the majority of patients. These observations led to the development of a novel therapeutic approach based on the use of rationally designed target-based agents that distinguish cancer from non-cancer cells. The process through which these new drugs are developed is requires that the target first be identified which is usually represented by a protein that is important for tumor cell proliferation, survival, invasion or resistance to conventional treatments, this is followed by the development of specific inhibitor, which is followed by pre-clinical studies to determine whether the inhibitor has an anti-tumor effect by using in vitro and/or in vivo models (p. 13, cols 1 and 2). This is followed by studies to confirm that the antitumor activity of these compounds is due to their ability to hit the specific target. Several lines of evidence suggest that the EGFR represents an ideal target for novel therapeutic approaches for human carcinomas. In fact, a majority of human solid tumors, including liver, express high levels of EGFR. Both in vivo studies and studies in experimental animal models have demonstrated the role played by EGFR in human carcinomas. EGFR has long been established as a target for molecules that modulate/inhibit the receptor (p. 14, col 1), wherein a number of receptor inhibitors have shown to have efficacy in treating cancer (p. 15, col 1).

Slesak et al teach that EGFR is overexpressed in gastric cancer.

Wong et al teach that nucleic acid encoding LI /cadherin/cadherin 17, which is expressed during intestinal development, but absent in normal stomach and liver tissue (p. 619), is expressed in the majority of gastric adenocarcinoma as well as in hepatocarcinoma in human tumor samples compared to normal control (see abstract). The reference teaches that induction of cadherin expression that is normally absent in the tissue appears to be involved with carcinogenesis (p. 624). Taken together, the data suggests that LI-cad is a potential

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

disease marker for HCC (see abstract) and by inference for gastric carcinoma.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have identified a mammal that will respond therapeutically to a method of treating cancer comprising administering an EGFR modular comprising measuring the level of SEQ ID NO:1/cadherin 17/LI-cadherin in the mammal, exposing the mammal to EGFR modulator and then remeasuring the assayed EGFR inhibitors in mammals, wherein a reduction of the level of the assay protein indicates that the mammal will respond therapeutically to said method of treating cancer because Normanno et al teach that EGFR is a conventional and successful target for anti-cancer treatments and that the efficacy of EGFR treatments is conventionally tested in animal studies of animals that express the target of interest. It would have been particularly obvious to measure the efficacy of the treatment by assaying, in either gastric or hepatocarcinoma animal models, the expression of nucleic acid encoding LI cadherin/cadherin 17 to identify mammals that would benefit from the treatment because Wong et al specifically teach that LI cadherin/cadherin 17 mRNA is differentially expressed in cancer cells compared to normal cells and appears to be a marker for the two cancer types and reduction of the expression of the marker/nucleic acid known to be differentially expressed in cancer cells compared to normal cells, would clearly be an indication that cancer cells expressing said marker had been reduced/killed that the therapy is effective, and that the mammal will respond therapeutically to the method of treating cancer. Although Wong does not specifically state that the LI cadherin/cadherin 17 is SEQ ID NO:1, given that the nucleic acid assayed encodes human LI cadherin/cadherin 17, given that it comes from the same source, it appears to be the same molecule, absent a showing a patenable differences. Further, it would have been prima facie obvious to assay for the marker in vitro given that assay in vivo would require anesthetizing the animal model and take time and material not necessary to the final outcome.

CHAPTER I
PCT TELEPHONE MEMORANDUM
FOR
LACK OF UNITY OF INVENTION

PCT No.: PCT/US05/00638

Examiner: Susan Ungar

Attorney spoken to: Paul Golian

Date of call: 21 June 2007

☐ Amount of payment approved:

☐ Deposit account number to be charged:

☐ Attorney elected to pay for ALL additional inventions

☐ Attorney elected to pay only for the additional inventions covered by

☐ Group(s):

-- encompassing –

☐ Claim(s):

☒ Attorney elected NOT to pay for any additional inventions, therefore, only the first claimed invention (Group I) covered by Claim(s) 1-in-part, 2, 3-in-part has been searched.

☒ Attorney was orally advised that there is no right to protest for any group not paid for.

☒ Attorney was orally advised that any protest must be filed no later than 1 month from the mailing of the Search Report (PCT/ISA/210).

Time Limit For Filing A Protest

Applicant is hereby given 1 month from the mailing date of this Search Report in which to file a protest of the holding of lack of unity of invention. In accordance with PCT Rule 40.2, applicant may protest the holding of lack of unity only with respect to the group(s) paid for.

Detailed Reasons For Holding Lack of Unity of Invention:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1 In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group 1, claims 1-in part, 2, 3-in-part drawn to a method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering an EGFR modulator, wherein the method comprises measuring in the mammal the level of SEQ ID NO:1, cadherin 17, wherein a difference in level of SEQ ID NO:1 is indicative that the mammal will respond to said method of treating cancer.

Note: A copy of this form must be attached to the Search Report.

Groups 2-125, claims 1-in part, 2, 3-in-part drawn to a method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering an EGFR modulator, wherein the method comprises measuring in the mammal the level of at least one biomarker selected from the 125 biomarkers disclosed in Table 1, other than SEQ ID NO:1, cadherin 17 wherein a difference in said biomarker or combination of biomarkers is indicative that the mammal will respond to said method of treating cancer. Additional fees must be paid for the search for the claimed method using of each individual biomarkers or biomarkers in combination.

A international stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. Unity of invention is fulfilled only when there is a technical relationship among the inventions involving one or more of the same or corresponding special technical features which define a contribution over the prior art. If there is no special technical feature, if multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(d). After that, all other products and methods will be broken out as separate groups (see 37 CFR 1.475(d).)

An international stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. When claims to different categories are present in the application, the claims will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories: (1) A product and a process specially adapted for the manufacture of said product; or (2) A product and a process of use of said product; or (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or (4) A process and an apparatus or means specifically designed for carrying out the said process; or (5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process. If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(b) and (d). Group I will be the main invention. After that, all other products and methods will be broken out as separate groups (see 37 CFR 1.475(d).)

Group 1 is drawn to a method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering an EGFR modulator, wherein the method comprises measuring in the mammal the level of SEQ ID NO:1, cadherin 17, wherein a difference in level of SEQ ID NO:1 is indicative that the mammal will respond to said method of treating cancer.

Groups 2-125 do not form a single inventive concept with the invention of Group 1 because they are drawn to additional methods and products used in those methods..

Accordingly, Groups 1-125 are not so linked as to form a single general inventive concept.

ATTACHMENT TO CHAPTER I PCT TELEPHONE MEMORANDUM FOR LACK OF UNITY OF INVENTION

Note: A copy of this form must be attached to the Search Report.